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13. ABSTRACT (Maximum 200 words)

Three lines of study were outlined in the previous report: 1) to test the efficacy of the catecholamine precursor L-Tyrosine in reducing pilot performance deficity caused by sleep deprivation, 2) to assess the role of endogenous melatonin on various performance and behavioral indices through photic modulation of nocturnal melatonin secretion and 3) to examine the effects on the same performance and behavioral variables of exogenous melatonin administered during the day. The data have been collected for all three studies, involving 14, 24, and 21 human volunteers respectively, and analysis is in progress. Preliminary analysis of the results are consistent with the hypotheses upon which the studies were predicated and provide a basis for a more fruitful continuation and elaboration of this investigation.

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Report AFOSR-90-0125

Strategies to Sustain and Enhance Performance in Stressful Environments

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ABSTRACT

Three studies were proposed under this grant. Study I was designed to determine the efficacy of the catecholamine precursor, L-Tyrosine in reducing pilot performance deficits caused by a night of sleep deprivation. Study II was conducted to examine the relationship between photically modulated nocturnal levels of the pineal hormone, melatonin, and performance. Study III was designed to examine relationships between graded doses of authentic melatonin, administered during the day, and human performance. Data collection for studies I, II, and III were completed in December, March and May of 1992 respectively. The data for Studies I and III will be reduced to manageable form, analyzed, and published throughout 1992. Data analysis for Study II is in the final stages and a manuscript should be finished in early 1992.

A) This project involves three separate studies. The objectives of each study are as follows:

The objectives of Study I:

1. To determine if the neurotransmitter precursor tyrosine can alleviate some of the fatigue and impaired performance that occur when simulated missions are flown by pilots after a night without sleep. Changes in vigilance, reaction time and mood state that occur during the simulated mission will be compared to simulator performance parameters to determine if any of these behaviors are facilitated by tyrosine administration.
2. To evaluate changes in auditory evoked potentials and the EEG that occur during the simulated mission and evaluate the effects of tyrosine on these parameters.
3. To study changes in levels of various urinary catecholamines, metabolites and stress hormones during the study and determine if tyrosine administration alters these.
4. To determine if administration of tyrosine alters some of the cardiovascular consequences of stress in humans.
5. To determine if tyrosine administration has any adverse effects on the ability of pilots to fly simulated missions, or on any other behavioral or physiological variables examined. This will provide information on whether tyrosine can be used safely in similar follow-up studies.
6. To compare results from a specific battery of laboratory tests of performance and mood with concurrent performance on the flight simulator.
7. To evaluate the utility of the flight simulator paradigm combined with sleep deprivation for assessing interventions that may alleviate stress.
8. To gather performance accuracy and variability data throughout an extended mission "flown" in a realistic but controlled environment. These data will provide a base performance level for future extended mission studies and could also provide new indices of performance deterioration.

The objectives of Study II:

1. To determine if the suppression of release of the hormone melatonin induced by bright light improves task performance and general alertness during the nadir of the circadian rhythm (sleep cycle). Alterations in vigilance and reaction time (visual and auditory) task performance, mood state, core temperature, and EOG that may result from the suppression of melatonin secretion will also be evaluated.
2. To determine if effects of bright light on these behaviors are "dose" dependent. That is, if varying the

intensity of the light used to suppress melatonin release causes a corresponding change in behavior.
3. To determine how changes in plasma melatonin concentration are related to corresponding alterations in behavior.
4. To evaluate psychological, physiological, and performance changes induced by the suppression of melatonin release and thus facilitate the application of this technology to areas of direct benefit to the USAF.
5. To evaluate the usefulness of testing procedures and facilities for a future long term study of the use of light as an aid to circadian rhythm resynchronization during shifting work/sleep cycles.

The objectives of Study III:

1. To determine if raising plasma levels of the hormone melatonin by administering exogenous melatonin decreases task performance levels and general alertness during the peak of the circadian rhythm (day-active cycle). This will be done by simultaneously evaluating alterations in vigilance and reaction time (visual and auditory) task performance, and mood state that may result from increasing plasma melatonin levels beyond their normal levels.
2. To determine if effects of exogenous melatonin on these behaviors is "dose" dependent. That is, if varying the plasma melatonin level causes a corresponding change in behavior.
3. To determine how changes in plasma melatonin concentration are related to corresponding alterations in behavior.
4. To evaluate psychological, physiological, and performance changes induced by increased plasma melatonin levels and thus facilitate the application of this technology to areas of direct benefit to the USAF.

B) Work on the three studies has progressed as follows (since Dec. 15, 1990):

Study I:

1. Dr. Dollins traveled to San Antonio, TX and remained there from July 15 through November 15 of 1991. Unfortunately, the beginning of subject testing was unexpectedly delayed due to a construction project which made it necessary to move the T40 flight simulator to another section of Building 170. Further delays were experienced while the simulator hardware was reassembled and debugged.
2. The flight simulator performance assessment software was modified and debugged. The flight tasks were linked

into continuous segments to be used throughout testing.

3. The data for twenty 27-hour testing sessions were collected prior to Dr. Dollins departure. Dr. Jon French completed the data collection for an additional 8 testing sessions to allow 14 subjects to complete testing.
4. Data collection was completed on December 23, 1991.
5. Initial data reduction (i.e., translation of computer files from binary to ASCII format) of the flight performance data has been performed. Analysis of this data is proceeding.
6. The sleep-deprivation/sustained flight paradigm was successful in producing subject fatigue and flight performance degradations.
7. Initial examination of the data indicate that physiological measures (i.e., oral temperature, blood pressure, and heart rate) did follow normal circadian patterns but were not affected by L-Tyrosine treatment.

Study II:

1. Twenty-seven subjects participated in testing between November 15 and March 20. Twenty three of the subjects completed all three of the required 13.5 h (i.e., 1630 - 0800 h) test sessions.
2. The three levels of bright light used in this study did differentially suppress melatonin secretion in all of the subjects tested.
3. There was marked inter-individual variability in melatonin secretion and suppression.
4. While a few analyses have yet to be conducted, our conclusions thus far are that behavioral changes attributable to melatonin are inextricable from the effects of exhaustion that necessarily accompany this type of testing.
5. There was no dose-dependent relationship between the light intensity used to suppress melatonin secretion and behavior as measured by the battery of performance tasks used.

Study III:

1. Twenty subjects participated in testing between March 27 and May 31. Each of the subjects completed five 09:30 to 17:00 h test sessions.
2. The doses of exogenous melatonin administered (ranging from 10 to 80 mg p.o.) at mid-day resulted in supra-physiological elevations in circulating melatonin concentrations that persisted throughout the 7-hour period of study. The mean serum melatonin levels were elevated in the expected dose-dependent manner. While the patterns of uptake and elimination over this extended dose range were similar, there were, again, marked inter-individual quantitative differences in

melatonin availability.

3. While statistical analysis has not been performed, plots of the data suggest that there are performance differences between placebo and all four levels of melatonin treatment tested. That is, 10 mg p.o. appears to be just as effective as 80 mg p.o. These differences appear in the self-reported Stanford Sleepiness, POMS Vigor/Activity, POMS Fatigue/Inertia, and POMS Confusion/Bewilderment Scales as well as the Latency of Correct Answers, Number of Premature Responses, and Number of Timeout Errors on the Four Choice RT. The same pattern of differences is evident in Oral Temperatures, but not in heart rate or blood pressure.

C) List of all AFOSR - related manuscripts (SPEC. IN 1991)

Burns, J.W., Werchan, P.M., Fanton, J.W., Dollins, A.B. (1991). Performance recovery following +Gz-induced loss of consciousness. Aviation Space & Environmental Medicine, 62, 615-617.

Deng, M.H., Lopez G., Coviella, I., Lynch, H.J., Wurtman, R.J. (1991). Melatonin and its precursors in Y79 human retinoblastoma cells: effect of sodium butyrate. Brain Research, 561, 274-278.

Dollins, A.B., Lynch, J.J., Deng, M.H., Wurtman, R.J., & Lieberman, H.R. (1991, November 10-15). Effects of bright light on human nocturnal performance, mood and serum melatonin levels. Paper presented to the Society for Neurosciences, New Orleans, LA.

Dollins, A.B., Lynch, H.J., Deng, M.H., Wurtman, R.J., & Lieberman, H.R. (1991, June 13-14). Effects of ambient illumination on human nocturnal serum melatonin levels and on sustained performance. Paper presented at the annual meeting of the Society for Light Treatment and Biological Rhythms, Toronto, Canada.

D) Professional Personnel associated with research effort:

Richard J. Wurtman, M.D.
Harry J. Lynch, Ph.D.
Andrew B. Dollins, Ph.D.
Mei Hua Deng, M.S.
Jon French, Ph.D. (AL/CFTO, Brooks AFB)
William F. Storm, Ph.D. (AL/CFTO, Brooks AFB)

E) Interactions:

i. Dr. Lynch presented a paper entitled "Effects of bright light on human nocturnal performance, mood and serum

melatonin levels" at the annual meeting of the Society for Neurosciences in New Orleans LA, November 10-15, 1991.

ii. Dr. Dollins presented a paper titled "Effects of ambient illumination on human nocturnal serum melatonin levels and on sustained performance" at the annual meeting of the Society for Light Treatment and Biological Rhythms, Toronto, Canada, June 13-14, 1991.

iii. Dr. Dollins traveled to Brooks AFB, San Antonio, TX, to conduct the T40/Tyrosine in association with Drs. Storm and French and AL/CFTO support personnel, July 15 - November 15, 1991.

F) Comments for AFOSR Program Manager.

A time line for the work we project for the next year can be found on the following page. This includes publication of the following studies: 1) The LBNP study conducted under AFOSR-87-0402; 2) The Light/Melatonin study (Study II above); 3) The Dose/Melatonin (Study III above); 4) The T40/Tyrosine Study (Study I above). In addition, we propose to conduct pilot work to further investigate the performance dose-response curve to exogenous melatonin using a lower dose range than that used in Study III above. In view of observations from our current melatonin studies, it is possible that the techniques we have used are not sufficiently discriminating to precisely detect the relationship between performance and serum melatonin levels. Toward the end of the year, we will initiate studies using psychophysical techniques for collection and analysis of performance data collected from subjects with varying serum melatonin levels and thereby further our understanding of the effects of exogenous melatonin.

Time Line for AFOSR Final Report

	J	F	M	A	M	J	J	A	S	O	N	D
AFOSR 1990 Annual Report	<>											
Write 93-95 Grant Proposal		<---->										
Write Paper on LBNP/Tyrosine Study	<->											
T40/Tyrosine Study Data Analysis	<------>											
Melatonin/Dose Study Data Analysis	<---------->											
Write Paper on Melatonin/Light Study		<-->										
Write Paper on T40/Tyrosine Study				<---->								
Write Paper on Melatonin/Dose Study							<--->					
Mel/Dose Study II Pilot Stdy Subj Tst							<--->					
Mel/Dose Study II Pilot Stdy Data Anl.								<-->				
Begin Mel/Dose Study II Subject Testing										<------		